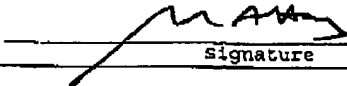


4/ Election

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	<u>April 17, 2003</u>
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**PATENT APPLICATION**  
**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : LIEBESCHUETZ, John Walter  
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ENGEL, David Birenbaum  
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Bet  
4-22-03

Serial No. : 10/030,189  
Filed : 04 February 2002  
Group Art Unit: 1625  
Examiner : CHANG, Celia  
For : Serine Protease Inhibitors  
Docket No. : 00220/US

Assistant Commissioner for Patents  
Washington DC 20231  
United States of America

Serial No. 10/030,189

Sirs

**Response to Restriction Requirement**

This communication is being filed in response to the Office Communication dated March 19, 2003, Paper Number 3.

**Restriction Under 35 U.S.C. 121 and 372**

The Examiner requires restriction of the application under 35 U.S.C. 121 and 372 and in accordance with 37 C.F.R. 1.499 as between the following two groups of inventions:

Group I: Claims 23, 35 and generic claims 1-16, 19-22, 24-25, 29, 31-34 reading on compounds with a piperidinyl core.

Group II: Claims 1-16, 19-22, 24-25, 29, 31-34 reading on compounds without a piperidinyl core.

Thus, referring to formula (I) in Claim 1, it is understood that the Examiner requires restriction between compounds of formula (I) in which q is 2 (piperidinyl compounds) and compounds of formula (I) in which q is 1 (pyrrolidinyl compounds).

Applicants hereby elect, to prosecute the inventions of Group I (the piperidinyl compounds), but respectfully request that the restriction requirement be reconsidered.

In the reasons given for requiring restriction of the application, the Examiner cites Example 78 in US 6,262,069, which is a national stage patent of WO 99/11657 and asserts that the compound of Example 78 of this patent anticipates Claim 1.

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It is respectfully submitted that the compound of Example 78 in US 6,262,069 does not anticipate Claim 1. The compound of Example 78 contains a prolinyl group, which has a carboxyl group attached to pyrrolidinyl. The compounds of Claim 1 do not have an attached carboxyl group. Furthermore, Claim 1, in the definition of  $R_2$ , contains a proviso that  $R_2$  cannot be aminoisoquinolyl. This proviso distinguishes the compounds of the present invention from the compounds of US 6,262,069. The present specification, at page 3, lines 1 to 14 acknowledges that WO 99/11657 discloses aminoisoquinoline compounds.

US 6,262,069, in fact, contains examples of piperidine compounds. The Examiner's attention is drawn in particular to the compound of Example 22. This compound corresponds with formula (I) in Claim 1 of the present application where  $R_2$  is aminoisoquinolyl, X-X is CONH, Y is CH (and is in the D configuration), and in the group represented by  $L-Lp(D)_n$ , q is 2, Q is O and  $R_q$  is phenyl.

For these reasons, Applicants respectfully request the Examiner to reconsider the restriction requirement (37 C.F.R. 1.143).

#### Election of Species

The Examiner has required the Applicants to elect a single species for examination, seemingly under 37 C.F.R. 1.499.

Applicants hereby elect the compound of Example 22a. Currently claims 1-3, 5, 7-16, 19-25, 29, 31-33 and 35 read on this compound. The compound corresponds with formula (I) in which  $R_2$  is indol-6-yl, X-X is CONH, Y is CH (and has the D-configuration), Cy is phenyl, and in the group represented by  $L-Lp(D)_n$ , q is 2, Q is O and  $R_q$  is pyrid-4-yl.

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It is respectfully submitted that the election of species requirement ought to be made under 37 C.F.R. 1.146, not 37 C.F.R. 1.499, which applies only to the election of the restriction group. An election of species requirement is different from a lack of unity (restriction) requirement, because it does not give rise to the consequences for filing divisional applications provided in 35 U.S.C. 121.

#### Claim to Priority

Applicants have noted that the Examiner has not checked any of the boxes in the section "Priority under 35 U.S.C. §§ 119 and 120" in the form PTO-326. Applicants would be grateful if the Examiner could confirm that the certified copies of the priority documents have all been received from WIPO. The filing receipt for the application does acknowledge Applicant's claim to priority.

#### Background Information

For the assistance of the Examiner, the following background information about this application is being provided. The Examiner will appreciate from the following that the undersigned is sorting out a very complex business and legal situation involving applications and patents now owned by two different companies. The undersigned apologizes to the Examiner for this complexity and for the lack of a timely filed information disclosure statement in this application.

This application is part of an international portfolio of patent applications protecting serine protease inhibitors, all of which are in the care of the undersigned. Some of these applications (including US 6,262,069 cited by the Examiner) now belong to Tularik Limited, a subsidiary of Tularik Inc in South San Francisco, and some of them now belong to Eli Lilly and Company in Indianapolis. The history

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of all of these applications traces back to a research project on serine protease inhibitors started by a small company in the undersigned's home town, Macclesfield, U.K., known as Proteus (later Protherics) Molecular Design Limited. The original applications encompassed benzamidine and aminoisoquinoline compounds, and now belong to Tularik Limited. As the research effort has continued and involved researchers at other sites, two different directions have been followed. One direction has led to compounds that are selective for the serine protease, trypsin. These compounds generally possess an aminomethylphenyl group, and are protected by Tularik applications. The other direction has led to further compounds that are selective for the serine protease, Factor Xa. These compounds are protected by Lilly applications. The claims in the Lilly applications have generally been drafted so that aminomethylphenyl compounds are not covered. Thus, all but one contain a proviso excluding aminoalkyl-substituted compounds (The Examiner is referred to the definition of  $R_1$  in Claim 1 of the present application). The one exception, Serial No. 09/926,716, which contains generic method claims reading on both aminomethylphenyl and non-aminomethylphenyl compounds, is intended to be abandoned.

In order to assist the Examiner to have a complete picture of the portfolio, a listing of all co-pending U.S. applications and patents in the portfolio is attached. When the Examiner inspects these co-pending applications, she will note that in the more recent applications, including the present application, the claimed inventions are further distinguished one from another by the definitions of the group  $L-Lp(D)_n$ .

Thus, the first applications filed in the portfolio were WO 99/11657 and WO 99/11658, directed to aminoisoquinoline and benzamidine compounds. US 6,262,069 is a national stage patent of WO 99/11657. Serial number

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09/988,082, which the Examiner is also examining, is a continuation-in-part of WO 99/11658, and also of WO 00/77027, as described below.

Next came three PCT applications, all filed on the same day and claiming priority back to common priority documents: WO 00/76971, WO 00/77027 and WO 00/76970. WO 00/77027 claimed aminomethylphenyl compounds. It has not entered the national stage, but as described above, serial number 09/988,082 is a continuation-in-part of this application. WO 00/76971 claimed compounds which do not have an aminomethylphenyl group (see the proviso in the definition of  $R_1$ ) or an aminoisoquinoline group (see the proviso in the definition of  $R_2$ ). It has entered the US national stage as serial number 09/926,712. WO 00/76970 contained method of use claims reading on the compounds of WO 00/77027 and WO 00/76971. It has entered the national stage as serial number 09/926,716 and has been allowed, but is intended to be abandoned.

Next came four more PCT applications: WO 01/96303, WO 01/96304, WO 01/96323 and WO 01/96296, all claiming priority back to WO 00/76971. The present application is the national stage of one of these applications. The Examiner will note from the file for the national stage of WO 00/76971, serial number 09/926,712, that the claims have been amended in that application so as to exclude the compounds now claimed in the present application.

Two further PCT applications were also filed and have entered the national stage: WO 01/44226 and WO 01/96305. These claim aminomethylphenyl compounds, and claim priority back to WO 00/77027.

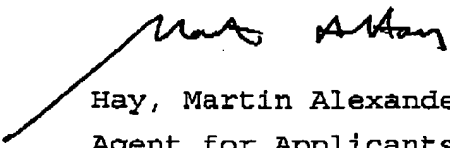
Thus, having regard to the definitions of  $R_2$  and L-Lp(D)<sub>n</sub> in Claim 1 of the present application, and in particular to the provisos excluding compounds in which  $R_2$  is aminoisoquinolyl and  $R_1$  is aminoalkyl, and to the amendments

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made in the claims of co-pending application serial number 09/926,712, it is believed that the claims in the present application are distinguished from the claims in the other Tularik and Lilly patents and applications.

Favorable consideration of the application is earnestly sought.

Respectfully submitted,

  
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April 17, 2003

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**Co-Pending Lilly and Tularik Applications and Patents**

**Co-pending applications - Assigned to Eli Lilly and Company**

09/926,712 (national stage of WO 00/76971)

09/926,716 (national stage of WO 00/76970 - intended to be abandoned)

10/030,188 (national stage of WO 01/96303)

10/030,186 (national stage of WO 01/96304)

10/030,187 (national stage of WO 01/96323)

10/030,189 (national stage of WO 01/96296)

**4. Co-pending applications and patents - Assigned to Tularik Limited**

US 6262069 and US 6420438 (national stage of WO 99/11657 and continuation)

09/988,082 (continuation-in-part of 09/485,678, WO 99/11658 and of WO 00/77027)

10/148,174 (national stage of WO 01/44226)

10/296,245 (national stage of WO 01/96305)



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### FACSIMILE TRANSMITTAL SHEET

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APR 17 2003

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**GROUP 1600**

Acknowledgment Requested: Yes No

#### Message:

Applicant : Liebeschuetz, John Walter, et al  
Serial No. 10/030,189  
Our Ref: 00220/US

Please find attached a response to the Office Action dated March 19, 2003.

  
Martin A. Hay, Reg. No. 39,459

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